

REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Specification

Applicants hereby submit a new Figure 1D that has a visible letter "C". Applicants also submit replacement for Figures 4A-4D and amend Brief Description of the Drawings for Figures 4A-4D to remove addition of new matter.

The 35 U.S.C. §112 Rejection

Claims 20-23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The present invention provides data that indicate Corticotropin Releasing Factor Receptor 2 (CRFR2) null mutant mice exhibit an increase in the size and number of blood vessels in various tissues. Since CRFR2 receptor and its activity have been localized

within the endothelial cell layer of blood vessels, the data presented herein indicate that CRFR2 plays a significant role in regulating angiogenesis. In view of the data disclosed herein, one of ordinary skill in the art would conclude that well-known CRFR2 agonists such as urocortin and CRF could be used to inhibit angiogenesis.

The Examiner contends that undue experimentation is required to practice the instant invention. Applicants respectfully disagree. Applicants submit that common methodologies of drug treatment such as IV infusion that are well known in the art can be used in the instant invention. For treatment of cardiovascular disease, one of ordinary skill in the art would readily employ methods of local transfer. It is well known in the art that local transfer of agent by perivascular or intravascular delivery provides a way of enhancing arterioprotective endothelial functions without stimulating neovascularization at other sites (Laitinen et al., *Human Gene Therapy* 8:1737, 1997).

Based on the data contained herein, Applicants respectfully submit that the claims on the method of inhibiting angiogenesis have reasonable correlation to the scope of the enablement provided by the specification. Accordingly, Applicants

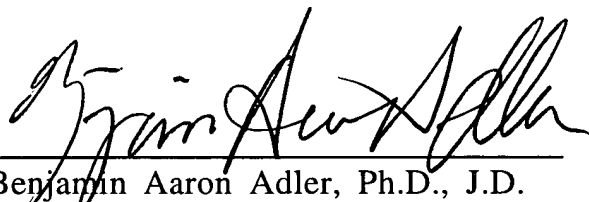
respectfully request that the rejection of claims 20-23 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action mailed March 20, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

In the section of BRIEF DESCRIPTION OF THE DRAWINGS, the descriptions for Figures 4A-4D have been amended as follows:

Figure 4A shows the percentage of time spent in the open arms (**, $p < 0.005$) and number of entries to the open arms (*, $p < 0.02$) were significantly less for the male mutant mice than for the wild type controls (control $n=7$, mutant $n=7$; mean \pm SEM).

Figure 4B shows the ~~percentage of time spent in the open~~ arms (*, $p < 0.03$) and ~~number of entries to the open arms~~ (*, $p < 0.03$) ~~were significantly less for the female mutant mice than for the wild~~ type controls (control $n=9$, mutant $n=12$; mean \pm SEM). locomotor activity was not different between control and mutant animals as measured by total closed arm entries and total arm entries.

Figure 4C shows ~~locomotor activity in the EPM was not~~ different between control and male mutant animals as measured by ~~total closed arm entries and total arm entries.~~ no difference was found in anxiety-like behavior as measured in the light/dark box experiment for time spent in the light portion of the box.

Figure 4D shows ~~locomotor activity in the EPM was not~~
~~different between control and female mutant animals as measured by~~
~~total closed arm entries and total arm entries.~~ no difference was found
in anxiety-like behavior as measured in the light/dark box
experiment for the number of transitions between the light and dark
portions.